Remarks

Amendments to the Claims

Claims 33, 41, and 55 were amended to define a pharmaceutical composition comprising: a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is capable of sublingual or buccal absorption through the mucous membranes of the mouth in a therapeutically effective level, wherein the intraoral portion is a film coating or a compression coating, and a second oral portion located within the first portion which contains a pharmaceutically active ingredient, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation. Support for the amendment is found, for example, on page 21, lines 22-24.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 41, 51, and 54 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

Legal Standard

Compliance with the first paragraph of § 112 is adjudged from the perspective of the person skilled in the relevant art. *Application of Smith*, 481 F.2d 910, 914 (CCPA 1973). The claimed subject matter need not be described in haec verba in the specification in order for that specification to satisfy the description requirement, *In re Smith*, 458 F.2d 1389 (CCPA 1972); *In re Lukach*, 442 F.2d 967 (CCPA 1971). "[T]he test for sufficiency of support in a parent

application is whether the disclosure of the application...reasonably conveys to the artisan that the inventor had possession at that time of the...claimed subject matter." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)(internal quotes and citations omitted). When the original specification accomplishes that, regardless of how it accomplishes it, the essential goal of the description requirement is realized. See, e. g., *In re Smythe*, 480 F.2d 1376 (CCPA 1973).

Analysis

The applicant describes the signaling system on page 15, line 5 to page 16, line 5 of the specification. The applicant discloses that the pharmaceutical compositions comprise a core, an outer coating layer and a signaling system interspersed between the outer coating and the core (page 15, lines 5-8). Other signaling systems which can be used include color changes of the dosage form, **gas liberation or effervescence**, changes in texture, changes in sensation, or local anesthesia (page 15, lines 22-25). Once the core is formed by blending, granulating, milling and compressing, a signaling system is applied to the surface of the core. The core is then ready for application of the coating containing the pharmaceutically active ingredient capable of intraoral administration (page 16, lines 1-5). The pharmaceutically acceptable signaling system may be located **in a separate layer between the first portion and the second portion** of the composition; within the first portion of the composition, or within the second portion of the composition (page 17, lines 16-19). The signaling agent may be coated on the inner core of the pharmaceutical compositions including the inner core of the composition in tablet form as well as immediately over the shell of the capsule containing the pharmaceutically active agent capable

of oral administration when the composition is in capsule form (page 28, lines 9-14). In both case, the first portion of the pharmaceutical composition containing the pharmaceutically active agent capable of intraoral administration **overlays the coating containing the signaling agent** (page 28, lines 14-17). Accordingly, the phrase "located between the first intraoral component and the second oral component" clearly has support in the specification.

Rejections Under 35 U.S.C. § 103

Claims 41, 51, and 54 were rejected under 35 U.S.C. § 103(a) as being unpatentable over GB 800,973 to Sterling ("Sterling"), in view of Remington's Pharmaceutical Sciences, 18th Ed. (1990), page 844 ("Remington"). Claims 33-39, 42-50, 52-53, and 55-57 were rejected under 35 U.S.C. 103(a) as being unpatentable over GB 800,973 to Sterling ("Sterling") in view of U.S. Patent No. 6,140,319 to Powell *et al.* ("Powell") in further view of DE 3338978 to Frömming ("Fromming"). Claims 33-43 and 49-57 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,053,032 to Barclay *et al.* ("Barclay") in view of U.S. Patent No. 6,200,604 to Panther *et al.* ("Panther"). Applicants respectfully traverse this rejection.

Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable

expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Analysis

Claims 41, 51, and 54 are not obvious over GB 800,973 to Sterling et al. ("Sterling") in view of Remington's Pharmaceutical Sciences ("Remington")

Claim 41 defines a pharmaceutical composition comprising:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient for uptake in the oral cavity in a therapeutically effective level,

the active ingredient having a molecular weight not exceeding 350 daltons or an active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration wherein the intraoral portion is a film coating which is applied to the core or a compression coating which is compressed around the core,

(b) a pharmaceutically acceptable effervescent agent which generates effervescence or a pharmaceutically acceptable signaling system, **located between the first intraoral component and the second oral component,** that is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid; and

(c) a second oral portion located within the first portion which contains a pharmaceutically active agent, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved.

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, the indicating lamination having an outer medicinal layer which is soluble in the patient's mouth. Sterling does not disclose a pharmaceutical composition comprising a pharmaceutically acceptable effervescent agent which

generates effervescence or a pharmaceutically acceptable signaling system, **located between the first intraoral component and the second oral component,** which is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid. Sterling also does not disclose a composition wherein the intraoral portion is a film coating applied to the core or a compression coating compressed around the core.

Remington discloses that nitroglycerin has a molecular weight of 227.09 and that for buccal tablets and sublingual tablets, the dose of nitroglycerin is 1 mg and 0.15-0.6 mg respectively. Remington does not disclose the elements missing from Sterling. The references must teach or suggest all the claims limitations. Therefore, the claims are not obvious over Sterling in view of Remington.

Claims 33-39, 42-50, 52-53, and 55-57 are not obvious over GB 800,973 to Sterling ("Sterling") in view of U.S. Patent No. 6,140,319 to Powell et al. ("Powell") in further view of DE 3338978 to Frömming ("Fröming")

Claim 33 defines a pharmaceutical composition comprising:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is capable of sublingual or buccal absorption through the mucous membranes of the mouth in a therapeutically effective level,

wherein the active ingredient is selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine,

Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration, whrein the intraoral portion is a film coating applied to the core or a compression coating compressed around the core; and

(b) a second oral portion located within the first portion which contains a pharmaceutically active ingredient, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

Claim 48 define the composition of claim 33 wherein the first intraoral component disintegrates or dissolves within 10 minutes, when the composition is contacted with saliva during intraoral administration.

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, the indicating lamination having an outer medicinal layer which is soluble in the patient's mouth. Sterling does not disclose a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level, wherein the active ingredient is

selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, *being present in an amount between 1 micrograms and 50 mg*, and having a rapid onset following intraoral administration.

Sterling also fails to disclose a second component which is either chewable or provides sustained release. Sterling describes a composition comprising an enteric coating such as shellac. An enteric coating delays release of the active agent until the dosage form reaches the intestine (page 24, lines 19-23, page 25, lines 10-14)). In contrast, a sustained release composition is one in which the drug is released over an extended period of time, for example 0.5 to 24 hours (page 23, lines 21-26). Delayed release is not the same as sustained release. Sterling does not disclose a composition wherein the second component is either chewable or provides sustained release.

Finally, Sterling does not disclose a composition wherein the intraoral portion is a film coating or a compression coating. Sterling describes compositions wherein the intraoral portion is **dusted** onto the core.

Powell describes the use of one or more vasopeptidase inhibitors to treat and/or relieve the symptoms of angina pectoris (col. 1, line 65 to col. 2, line 1). Preferred vasopeptidase inhibitors include omapatrilat and BMS 189,921. Typical dosages of the vasopeptidase inhibitors for treating angina range from 0.1 mg/kg to about 0.2 mg/kg, preferably from about

0.3 mg/kg to about 2.0 mg/kg (col. 3, lines 43-47). The vasopeptidase inhibitor(s) may be employed in combination with one or more pharmaceutically acceptable agents known to be useful in the treatment of angina such as long-acting nitrates such as nitroglycerin; β-adrenergic blocking agents such as propanolol hydrochloride, timolol maleate, carvedilol, and metoprolol tartrate; calcium entry blockers such as amlodipine besylate, diltiazem hydrochloride, and verapamil hydrochloride; and antiplatelet agents (col. 4, lines 5-15). Powell does not disclose or even suggest a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level; and a second oral portion located within the first portion which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

The Examiner alleges that it would have been obvious for one of ordinary skill in the art to look to the teachings of Powell and utilize the instant verapamil in place of Sterling's nitroglycerin since Powell teaches that both compounds are used to treat angina and the pharmaceutical forms include buccal and sublingual. Powell discloses that the **vasopeptidase inhibitor** is preferably administered orally in tablet or capsule form (col. 3, lines 59-60). Other methods of administration can be utilized including sublingually, bucally, parenterally, nasally, topically, transdermally, or rectally (col. 3, lines 60-67). Powell does not disclose or suggest the

use of verapamil or amlodipine for uptake in the oral cavity and Powell is silent regarding the dosages of the coadministered pharmaceutically active agents such as verapamil hydrochloride and amlodipine.

Frömming describes the use of verapamil or gallopamil for sublingual or buccal administration. The verapamil or gallopamil can be administered in a tablet, a chewable capsule or a spray. For the production of sublingual tablets, the concentration of verapamil is from 5 to 25 mg. Frömming does not disclose a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level; and a second oral portion located within the first portion which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

In summary, the prior art discloses pieces of the claimed composition but not the motivation to combine or modify as applicants have done.

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, the indicating lamination having an outer medicinal layer which is soluble in the patient's mouth, but Sterling does not describe a composition having a second oral portion which is either a chewable or sustained release formulation nor a composition wherein the intraoral portion is a film coating applied to the core

or a compression coating compressed around the core. Sterling does not disclose the drugs recited in claim 33.

Powell and Frömming describe the use of one or more vasopeptidase inhibitors to treat and/or relieve the symptoms of angina pectoris, but not the motivation to combine with a second drug that is released later for absorption in the GI tract.

Nowhere does the prior art provide the motivation to combine these elements as applicants have done. It is well established that it is not sufficient to merely identify art and then assert that it would be obvious to combine: the motivation must come from the references.

Claims 33-43 and 49-57 are not obvious over U.S. Patent No. 5,053,032 to Barclay et al. ("Barclay") in view of U.S. Patent No. 6,200,604 to Panther et al. ("Panther")

Barclay describes an ***osmotic*** device for a delivering a drug into the mouth of a human patient (abstract). The device described by Barclay comprises a wall surrounding a compartment housing a layer of an agent that is insoluble to very soluble in aqueous biological fluids such as saliva and a layer of fluid swellable hydrophilic polymer. A passageway in the wall connects the agent with the exterior of the device. The wall is permeable to the passage of aqueous biological fluids but impermeable to the hydrophilic polymer. The device described by Barclay is designed to deliver the ***same*** drug into both the oral cavity and into the GI tract since the device has only ***one*** drug reservoir (see Figs. 1-4 and col. 8, lines 31-35). This device cannot be used to deliver two different drugs as described by the applicants and, therefore, is distinctly different.

Barclay does not disclose the use of a sustained release or chewable formulation which is swallowed. Barclay describes an osmotic device. Indeed, Barclay clearly teaches away from

either a sustained release or a chewable second portion. While Barclay describes one embodiment which contains an HPMC coating, such a coating may ***delay*** release of the second component, but it would not result in ***sustained*** release. Chewing would destroy an osmotic device.

Barclay's device is "designed to be retained in the mouth for periods of time on the order of 0.5 to 12 hours" (col. 7, lines 35-36). The applicants describe a composition wherein the first portion [that contains a drug to be released for uptake in the oral cavity into the systemic circulation] "disintegrates or dissolves within 10 minutes, when the composition is contacted with saliva" (see claim 48). Barclay indeed discloses a variety of drugs that can be delivered using the device (col. 10, line 50 to col. 11, line 35); however, only one drug can be delivered using the device. The drug can ***either*** be intended for uptake in the oral cavity or intended for uptake in the intestine. The applicants' composition allows for administration of drug intended for uptake in the oral cavity ***followed*** by drug intended for uptake in the intestine.

Applicants select and use drugs for uptake within the oral cavity based on their ability to be absorbed through oral mucosa membrane (structural features and/or relatively low molecular weights), and use a film or compressed coating as defined by the amended claims to result in very rapid release within the oral cavity. Barclay makes no distinction between two different classes of drugs: (a) drugs that are released for uptake in the oral cavity and (b) drugs that are released in the oral cavity and swallowed for uptake in the intestine. Applicants have designed a composition that can deliver drugs from both classes in a single dosage form.

Panther describes a pharmaceutical dosage form comprising an orally administerable medicament in combination with an effervescent agent used as a penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa (col. 2, lines 7-11). Panther discloses that the effervescent agent can act to increase the rate and extent of absorption of the active agent by: (1) reducing the mucosal layer thickness and/or viscosity; (2) tight junction alteration; (3) inducing a change in the cell membrane structure; and (4) increasing the hydrophobic environment within the cellular membrane.

One or ordinary skill in the art would not be motivated to combine the teachings of Barclay and Panther to make the claimed pharmaceutical composition, nor would one obtain the claimed composition by combining Barclay with Panther.

Claims 41, 51, and 54 are not obvious over U.S. Patent Application Publication No. 2001/0002999 to Neuser et al. ("Neuser") in view of U.S. Patent No. 5,053,032 to Barclay et al. ("Barclay")

Neuser describes pharmaceutical compositions which can be administered orally and contain a fixed combination of at least one ***locally*** acting analgesic with a rapid onset of action and at least one systemically acting analgesic with a sustained action.

Barclay is discussed above.

In contrast to Neuser, both active ingredients of the applicant's composition are ***systemically*** acting agents that are released into the blood stream at different sites in the human body: the first ingredient which is released rapidly through the use of a film or compressed coating within the oral cavity and the second ingredient within the intestine. Barclay, drawn to

an osmotic device, does not make up for this deficiency nor make obvious the claimed compositions.

Summary

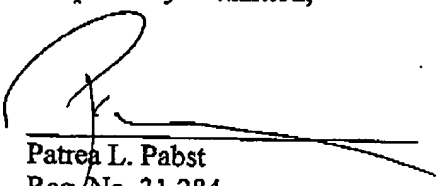
None of the prior art discloses nor leads one of ordinary skill in the art to the claimed composition. One can only arrive at the claimed composition using hindsight reconstruction. The art does not disclose the claimed elements as well as the motivation to combine as applicants have done, with a reasonable expectation of success for the intended purpose. Therefore the claims are not obvious over the cited art.

Double Patenting Rejection

Claims 33, 35, 38-39, 41, 43, 44, 46, and 48 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims Application Serial No. 10/015,930. In response, Applicants will file a terminal disclaimer to overcome the double patenting rejection upon indication that the claims are otherwise allowable.

Allowance of claims 33-57, as amended, is respectfully solicited.

Respectfully submitted,



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Date: December 22, 2005

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